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(54) Title: NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES		
(57) Abstract <p>There is described a device for the non-invasive measurement of one or more analytes in blood in a patient's body part which comprises a light transmitter comprising a plurality of transmitting fibres positioned to transmit light to the body part and a light detector comprising a plurality of light detector fibres positioned to detect light transmitted through or reflected from the body part. The device especially utilises the non-pulsatile element of a patient's blood. There is also described a method of measuring blood glucose levels and a device programmed so as to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation.</p>		

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NON-INVASIVE MEASUREMENT OF BLOOD ANALYTES

This invention relates to a novel monitor, particularly a monitor for the non-invasive measurement of glucose in eg diabetics and a method for determining glucose levels.

5

Diabetes mellitus (abbreviated to diabetes) is the name for a group of chronic or lifelong diseases that affect the way the body uses food to make energy necessary for life. Primarily, diabetes is a disruption of carbohydrate (sugar and starch) metabolism and also affects fats and proteins. In people who have diabetes the
10 glucose levels vary considerably being as high as 40 mmol/l and as low as 2 mmol/l. Blood glucose levels in people without diabetes vary very little, staying between 3 and 7 mmol/l. These levels follow the typical patterns shown in Figure 1a.

Hyperglycaemia (high blood glucose)

15 Both insulin dependant diabetes (IDDM) and non-insulin dependant diabetes (NIDDM) are associated with serious tissue complications^h which characteristically develop after 10-20 years duration of diabetes. Diabetic eye disease, retinopathy, is the commonest cause of blindness in western countries in people under the age of 65 years. Diabetic renal disease, nephropathy, is an important cause of kidney failure in
20 the community. Diabetic neuropathy affects the peripheral nerves causing impaired sensation and leg ulcers, and damage to the autonomic nervous system causes postural hypertension (low blood pressure on standing) and diarrhoea. Atherosclerosis is 2-4 times as high in diabetic as non-diabetic people and manifest as an increased frequency of myocardial infarction (heart attacks), cerebrovascular
25 disease (strokes) and the peripheral vascular disease (causing reduced circulation to the limbs and the risk of gangrene and amputation).

For many years it has been something of an article of faith in clinical diabetes that the cause of the complications is exposure of the tissues over many years to the
30 higher than normal blood glucose levels which have been usual in most treated diabetic patients. Conclusive proof of this theory has only recently become

available; the landmark Diabetes Control and Complications Trial (DCCT) in North America was announced in 1993 and showed that IDDM patients randomly assigned to an intensive and optimised insulin treatment programme designed to produce near-normal blood glucose levels had significantly less retinopathy, kidney disease and neuropathy over a 9-year period than patients assigned to ordinary treatment (ie poor control).

The DCCT has been a major stimulus to physicians around the world to renew efforts to improve control in diabetic patients, and to develop improved methods of obtaining good control and of monitoring these patients.

Hypoglycaemia (low blood glucose)

An important additional finding in the DCCT was that the frequency of hypoglycaemia was three-fold higher in the well-controlled patients than those with ordinary control. This confirms the long-standing appreciation by physicians that hypoglycaemia is extremely frequent in IDDM, and especially so in those that are well controlled. There are many reasons for this including mistiming of insulin injections and food, erratic absorption of insulin, and impaired secretion in some diabetic patients of the so-called counter regulatory hormones such as adrenaline and glucagon that oppose the action of insulin.

About one third of IDDM patients have no warning symptoms of hypoglycaemia (eg sweating, nausea, blurred vision, palpitations) and they rely on intermittent self-monitoring of blood glucose to detect dangerously low glucose levels. The consequences of hypoglycaemia include impaired cognition and consciousness, and eventually coma.

Since the late 1970's, an increasing number of diabetic patients, mostly IDDM, have been measuring their own blood glucose concentrations using finger-prick capillary blood samples. Self blood glucose monitoring (SBGM) is used by diabetics in the home to detect hypoglycaemia or hyperglycaemia and take corrective action such as

taking extra food to raise the blood glucose or extra insulin to lower the blood glucose. The measurements, which are made using a low-cost, hand-held blood glucose monitor (BGM), also allow the physician to adjust the insulin dosage at appropriate times so as to maintain near normoglycaemia.

5

BGMs use either reflectance photometry or an electrochemical method to measure the glucose concentration. Reflectance photometry measures the amount of light reflected from the reagent-impregnated test strip that has reacted with a drop of blood. The operator pricks the finger of the patient or earlobe with a sterile lancet or
10 uses anticoagulated whole blood collected in heparin and then places the blood on the test strip. The operator must place the blood onto the test strip at the time the monitor begins its timing sequence. This step is critical because under-timing (under-incubation) or over-timing (over-incubation) of the reaction may cause inaccurate measurements. At the audible signal, the operator wipes or blots the
15 excess blood off the outside of the test strip. The operator then inserts the strip into the monitor for measurement.

In the electrochemical method a disposable single-use enzyme electrode test strip is used. When the test specimen is placed onto the test strip, an enzymatic reaction
20 occurs that results in a current through the strip. The current is directly proportional to the concentration of glucose in the specimen.

The main disadvantages of SBGM systems are poor patient acceptance because the technique is painful, only intermittent assessment of diabetic control is possible and
25 readings during the night or when the patient is otherwise occupied such as during driving are not possible. It is estimated that less than half of the IDDM patients in the US perform SBGM.

Further, glucose values obtained with BGMs may not agree with clinical laboratory
30 results. Routine laboratory measurements of glucose are performed on either serum

or plasma venous blood specimens that correspond with glucose concentrations measured on whole blood glucose analysers.

Whole blood glucose values are lower than those obtained from either serum or plasma. Although glucose is not a static component in human blood, changes in blood glucose concentration following food intake in normal and hyperglycaemic conditions are reasonably predictable. Similarly, the variation in glucose concentration as blood passes from arteries or capillaries to veins has also been documented. Therefore, over time, repeated measurement of blood glucose from the same patient may diverge widely. Also, blood obtained simultaneously by finger stick and venipuncture may not have the same glucose concentration. (Venous blood may contain 1 mmol/l less glucose than capillary blood if the same samples are obtained within 1-2 hours after carbohydrate intake).

Furthermore, the haematocrit of the patient (the volume of cells, mostly erythrocytes, expressed as a percentage of the volume of whole blood in a sample) influences glucose values, and whole blood glucose measurements must be corrected for this. Unfortunately, because BGMs cannot automatically correct for the haematocrit of the patient, an error of 5-15% may be introduced.

There is widespread agreement that for self-monitoring in the home the reluctant acceptance of the current finger-stick method is the main reason why the development of a non-invasive measurement technique has such high priority.

A non-invasive measurement device is known from US Patent No 5,553,613. US '613 describes a technique which uses the pulsatile component of the light intensity transmitted through the finger, from which to derive the glucose concentration non-invasively. It does this by using the wavelengths 805nm, 925nm, 970nm and the range 1000-1100nm. The measurements were made by transmission, ie light was passed through the finger. However, as mentioned above, US '613 specifically relies upon the pulsatile component of the light transmitted through the patient. Such a

pulsatile technique has clear disadvantages in that the pulsatile component of the light signal, whether transmitted or reflected, is less than 2% of the total signal. Thus, prior art devices which use only the pulsatile component are much less sensitive and much more vulnerable to patient movement which can cause interference which is in the order of a few hundred times the relevant signal.

Moreover, the pulsatile signal identifies arterial blood specifically. Whilst this is advantageous when considering the pulmonary circulation of a patient, it provides no information on the patient's systemic circulation which is important for glucose determination. Further, pulsatile techniques are limited to use on body extremities, eg finger, ear lobe or the ball of the foot in babies or neo-nates.

The present invention overcomes or mitigates the disadvantages of the prior art by using a plurality of closely associated transmitters and generators which allows an "average" evened out signal to be produced and is capable of utilising the non-pulsatile element of the patient's blood flow. In addition, a further advantage of the invention is that it allows the measurement of oxygen saturation (SO_2). Furthermore, the invention permits the measurement of haemoglobin index (HbI) and/or temperature.

According to the invention we provide a device for the non-invasive measurement of one or more analytes in blood in a patient's body part which comprises a light transmitter comprising a plurality of transmitting fibres positioned to transmit light to the body part and a light detector comprising a plurality of light detector fibres position to detect light transmitted through or reflected from the body part.

A preferred embodiment of the invention is one wherein the non-pulsatile element of the patient's blood is utilised. Thus, according to a further feature of the invention we provide a device for the non-invasive measurement of one or more analytes in blood in a patient's body part as herein before described which is adapted to measure the non-pulsatile element of a patient's blood. In a further preferred embodiment the

device measures the pulsatile and non-pulsatile elements of a patient's blood. The device may be so adapted by being provided with a plurality of closely associated transmitters and generators which allows an "average" evened out signal to be produced.

5

Although various analytes may be measured, the detector of the invention is especially useful in measuring blood glucose level. We especially provide a device for the non-invasive measurement of one or more analytes in blood in a patient's body part as herein before described which is adapted to measure blood glucose levels.

10

The device may be capable of measuring other parameters either separately or in addition to blood glucose. An especially advantageous feature is the device may be adapted to measure blood oxygen saturation (SO₂).

15 As a further preferred embodiment we provide a device which is adapted to measure the haemoglobin index (HbI) and/or temperature of a patient's blood.

The device may be adapted for use, with any body part although it is preferable that it can be a finger or thumb.

20

The number of transmitter fibres may vary although we have found that 18 transmitter fibres works well. The number of detector fibres may be the same or different to the number of transmitter fibres, but may vary and we have found that 12 detector fibres works well. The diameter of the detector and the transmitter fibres may be the same or different and may vary, a diameter of 250µm is preferred.

25

The detector fibres are preferably positioned to detect reflected light rather than transmitted light.

30 The wavelength used in the transmitter fibres will generally be from 500 to 1100nm. However, it is a further feature of the invention to provide a detector as hereinbefore

described which also measures haemoglobin index (HbI) and/or oxygen saturation (SO₂) of blood. For such measurement, specific wavelengths are used, namely 500.9nm, 528.1nm, 549.5nm, 561.1nm, 572.7nm and 586.3nm. The preferred wavelengths for measuring blood glucose are from 800nm to 1100nm.

5

According to a further feature of the invention we provide a method of measuring blood glucose levels which comprises placing a non-invasive measuring device as hereinbefore described against a body part of a patient and using the detector to measure the light transmitted through or reflected from the body part.

10

In a yet further feature of the invention we provide a device according to as herein before described programmed so as to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation. Clearly, since blood oxygen saturation is dependent upon both the haemoglobin index and the oxygen

15 index, the computer is programmed so as to calculate these equations first if blood oxygen saturation is to be calculated.

We also provide a computer programme product comprising a computer readable medium having thereon computer programme code means, when said programme is

20 loaded, to make the computer execute a procedure to calculate one or more of the haemoglobin index, the oxygen index and the "whole blood" oxygen saturation as herein before described.

The invention will now be illustrated but in no way limited by reference to the

25 following example and drawings in which;

Figure 1 is a plot of the predicted glucose values against the measured glucose values; and

Figure 1a is a graph comparing normal blood glucose levels with those of a

30 diabetic.

Example 1

Glucose measurement

- In vivo* measurements using the MCPD spectrophotometer were carried out at 10 min intervals on the fingertips of 8 volunteers during the course of glucose tolerance tests and the results compared with those measured using a conventional blood glucose monitor. In addition, parallel measurements of local blood flow (laser Doppler flux) and temperature were made.
- The analysis which is presented here uses the same wavelength range used in the previous glucose studies carried out namely: 805nm, 925nm, 970nm and the broadband average 1000-1100nm, but additionally wavelengths sampled at regular intervals in the entire range 800nm to 1100nm. Intervals of 1.96nm worked well.
- Earlier work demonstrated that the glucose-dependent signal emanates from haemoglobin. Furthermore, although the 805nm wavelength could be used to compensate for small changes in haemoglobin concentration large changes continued to interfere with the sensitivity for glucose. It was furthermore recognised that changes in haemoglobin oxygenation would cause absorption changes from 800nm to 1100nm. As in all physiological measurements carried out in the peripheral circulation, temperature is also likely to be a controlling parameter. In the novel analysis carried out on the intensity spectra in the experiments carried out here, the three parameters haemoglobin concentration, oxygen saturation and temperature were introduced into the multiple linear regression analysis along with the near infrared parameters previously used.

Experimental

- 13 glucose tolerance tests (GTTs) were carried out on 8 different volunteers. In one case, 200ml water was given instead of the solution of 75g glucose in 200ml water; a real GTT was subsequently carried out on the same volunteer. In one volunteer five GTTs were carried out on separate occasions. One volunteer had diabetes.

All measurements were carried out with an Otsuka Optronics Photol MCPD-1000 photodiode array lightguide spectrophotometer. The 0.2mm slit was used for the diffraction grating giving a full width at half maximum transmission of 7.2nm, comparable with the glucose monitor. Using the supplied software, the instrument allows access to data points at 1.94nm intervals within the wavelength range 300-1100nm. The range displayed during the glucose experiments was 500-1100nm. In order to mimic the broad bandwidth characteristics of the previous glucose monitor above 1000nm, all measurements were averaged over the range 1000-1100nm. Quartz lightguides were used in conjunction with a 400W quartz-halogen light source.

A lightguide bundle, which consisted of 18 transmitting and 12 receiving fibres each of 250µm diameter, was attached to the fingertip of the subject by means of a laser Doppler probe holder. Recordings of spectra were made at 10 min intervals throughout the test using the MCPD spectrophotometer described above. These recordings were accompanied by parallel measurements of glucose concentrations in blood, obtained by pinprick of a contralateral finger with the aid of a Softelix pro lancet system, using a Boehringer Mannheim Advantage® glucose monitor. The lightguide was removed from the finger after each measurement and new dark and reference spectra recorded before each new measurement. A total of 13 measurements were carried out over a 2 hour period.

Careful selection of integrating time and the intensity of the reference spectrum enabled the simultaneous record of spectra that covered not only the range 800-1100nm, but also the visible range from 500-600nm. This enabled the evaluation of skin haemoglobin saturation (SO_2) and haemoglobin concentration (HbI) (Harrison DK *et al*, (1993) *Phys Meas* 14: 241-52) from the same spectra as those being analysed for glucose (see below).

30

A Moor Instruments DRT4 laser Doppler perfusion monitor was used to measure blood flow changes in the adjacent finger. The probe incorporated a thermal sensor, which was used to measure skin temperature (note: also on the adjacent finger) throughout the experiment.

5

Derivation of HbI and SO₂

HbI and SO₂ were derived from the absorption spectra measured from 500.8 to 586.3nm using a computer program VOXYG written for the purpose. The program carried out the following calculations.

10

Haemoglobin Index

$$\text{HbI} = ((b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6) * 100$$

15

Oxygenation Index

$$\text{OXI} = (e-d)/11.7 - (d-c)/11.6 * 100 / \text{HbI}$$

Oxygen Saturation

20

$$\text{SO}_2 = 100 * (\text{OXI} + 0.43) / 1.5$$

where a = absorption value at 500.9nm

b = absorption value at 528.1nm

25

c = absorption value at 549.5nm

d = absorption value at 561.1nm

e = absorption value at 572.7nm

f = absorption value at 586.3nm

30 MULTIPLE LINEAR REGRESSION ANALYSIS

A data file A was created containing the full absorption spectral data (800-1100nm in 1.96nm steps) from all 12 GTTs in the series. The absorption values in the file are defined in "absorption units" referred to here as ABUs. The other data contained in the file were time, experiment identification, glucose concentration (invasive), HbI, SO₂, temperature, and laser Doppler flux.

A number of secondary files were created whereby a sequence of "normalisations" of the data were performed:

- 10 • B - ABU data of A was normalised by subtraction of the absorption of the values at 802nm (ie $ABU_A - ABU_{802}$). This is similar to the way in which previous data was treated.
- C - ABU data of B was further normalised by division by the HbI value (ie ABU_B/HbI). This was designed to take into account of the results of the *in vitro* experiments which showed that normalisation at, then, 805nm did not fully compensate for changes in haemoglobin concentration.
- 15 • D - ABU data of C was further normalised by division by the SO₂ value (ie ABU_C/SO_2) to take into account the influence of changes in the relative concentrations of oxygenated haemoglobin (HbO₂) and deoxygenated haemoglobin (Hb) on the infrared spectrum.
- 20 • E - SBU data of D was yet further normalised by subtraction of the value at the assumed water peak (ie $ABU_D - ABU_{949}$) in an attempt to take into account changes in water content.
- 25 The types and orders of normalisations may vary, and the above are examples.

The above files were then subjected to multiple linear regression, analysis using SPSS for Windows 6.1.2. All of the wavelengths available in the above data files, ie 800nm to 1100nm in 1.96nm steps were entered as independent variables. The results of the multiple wavelength regressions are given below. The regressions

include only the spectral data and not HbI, SO₂ or temperature as further independent variables at this stage.

	r	Standard Error (SE) (mM)	No of Wavelengths Included
A	0.48	2.81	4
B	0.89	1.69	37
C	0.80	2.05	21
D	0.89	1.61	31
E	0.93	1.40	48

5 The predicted values from the last correlation using data file E are plotted against the measured glucose values in Figure 1. The predicted values are given as standardised to the mean and number of standard deviations on the left hand side of the y-axis and as mM on the right hand side.

10 The results obtained using the multi-wavelength analysis are significant improvements to those using the original parameters applied to the collective results. Figure 1 could indicate that the method may eventually allow a universal calibration, or at least one based on a particular individual, particularly if the ways in which the spectra are normalised are varied.

15

Above multiple regression analyses result in regression equations whose coefficients can be incorporated into an equation to produce a new parameter "calculated Glucose". This, together with the parameters HbI, SO₂ and temperature can then be incorporated into a further regression equation for each individual GTT.

20

Least squares fitting of mean "calibration spectra" recorded from the GTT series could be used for a universal or individual calibration.

25

CLAIMS

1. A device for the non-invasive measurement of one or more analytes in blood in a patient's body part which comprises a light transmitter comprising a plurality of
5 transmitting fibres positioned to transmit light to the body part and a light detector comprising a plurality of light detector fibres positioned to detect light transmitted through or reflected from the body part.
2. A device according to Claim 1 characterised in that it is adapted to utilise the non-pulsatile element of a patient's blood.
- 10 3. A device according to Claim 1 characterised in that it is adapted to utilise the non-pulsatile and the pulsatile elements of a patient's blood.
4. A device according to Claim 2 characterised in that it is so adapted by being provided with a plurality of closely associated transmitters and generators which
15 allow an "average" evened out signal to be produced.
5. A device according to Claim 1 characterised in that it is adapted to measure blood glucose levels.
6. A device according to Claim 1 characterised in that it is adapted to measure
20 blood oxygen saturation (SO₂).
7. A device according to Claim 1 characterised in that it is adapted to measure the haemoglobin index (HbI).
- 25 8. A device according to Claim 1 characterised in that it is adapted to measure the temperature of a patient's blood.

9. A device according to Claim 1 characterised in that it is adapted to measure two or more analytes in blood, which analytes are selected from blood glucose levels, blood oxygen saturation (SO₂), the haemoglobin index (HbI) and the temperature of a patient's blood.

5

10. A device according to Claim 9 characterised in that it is adapted to measure blood glucose levels, blood oxygen saturation (SO₂), the haemoglobin index (HbI) and the temperature of a patient's blood.

10 11. A device according to Claim 1 characterised in that it is adapted to measure of one or more analytes in blood in a patient's finger or thumb.

12. A device according to Claim 1 characterised in that it is provided with a greater number of transmitter fibres than detector fibres.

15

13. A device according to Claim 1 characterised in that it is provided with from 12 to 24 transmitter fibres.

14. A device according to Claim 13 characterised in that it is provided with 18
20 transmitter fibres.

15. A device according to Claim 1 characterised in that it is provided with from 6 to 18 detector fibres.

25 16. A device according to Claim 14 characterised in that it is provided with 12 detector fibres.

17. A device according to Claim 1 characterised in that diameter of the fibres is from 200 - 300µm.

30

18. A device according to Claim 1 characterised in that diameter of the fibres is 250µm.
19. A device according to Claim 1 characterised in that the detector fibres are positioned to detect transmitted light rather than reflected light.
20. A device according to Claim 1 characterised in that the wavelength used in the transmitter fibres is from 500 to 1100nm.
21. A device according to Claim 20 characterised in that the wavelength used in the transmitter fibres is from 800 to 1100nm.
22. A device according to Claim 21 characterised in that the wavelength used in the transmitter fibres is 805nm, 925nm, 970nm and the broadband average 1000-1100nm.
23. A device according to Claim 21 characterised in that the wavelengths are sampled at regular intervals of 1.96nm in the entire range 800nm to 1100nm.
24. A device according to Claim 20 characterised in that the wavelength used in the transmitter fibres is from 500 to 600nm.
25. A device according to Claim 20 characterised in that the wavelength used in the transmitter fibres is 500.9nm, 528.1nm, 549.5nm, 561.1nm, 572.7nm and 586.3nm.
26. A device according to Claim 20 characterised in that the wavelength used in the transmitter fibres is 500.9nm, 528.1nm, 549.5nm, 561.1nm, 572.7nm and 586.3nm; and from 800nm to 1100nm.

27. A method of measuring blood glucose levels which comprises placing a non-invasive measuring device as herein before described against a body part of a patient and using the detector to measure the light transmitted through or reflected from the body part.
- 5 28. A method according to Claim 27 characterised in that the non-pulsatile element is used.
29. A method according to Claim 28 characterised in that the non-pulsatile and
10 pulsatile element is used.
30. A device according to Claim 1 programmed so as to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation.
- 15 31. A device according to Claim 30 programmed so as to conduct a multiple linear regression analysis on spectral data collected by the detectors.
32. A device according to Claim 30 wherein the Haemoglobin Index is calculated using the equation:
20
- $$\text{HbI} = ((b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6) * 100$$
- where
- a = absorption value at 500.9nm
- b = absorption value at 528.1nm
- 25 c = absorption value at 549.5nm
- e = absorption value at 572.7nm.
33. A device according to Claim 30 wherein the Oxygenation Index is calculated using the equation:
30
- $$\text{OXI} = ((e-d)/11.7 - (d-c)/11.6) * 100 / \text{HbI}$$

where c = absorption value at 549.5nm
 d = absorption value at 561.1nm
 e = absorption value at 572.7nm.

5

34. A device according to Claim 30 wherein the Oxygen Saturation (SO_2) is calculated using the equation:

$$SO_2 = 100 * (OXI + 0.43) / 1.5.$$

10

35. A method of measuring blood oxygen saturation which comprises placing a non-invasive measuring device as herein before described against a body part of a patient and using the detector to measure the light transmitted through or reflected from the body part using a device according to Claim 34.

15

36. A computer programme product comprising a computer readable medium having thereon computer programme code means, when said programme is loaded, to make the computer execute a procedure to calculate one or more of the haemoglobin index, the oxygen index and the blood oxygen saturation.

20

37. A computer programme according to Claim 36 wherein the computer programme code means will make the computer execute a procedure to calculate one or more of :

25

$$HbI = ((b-a)/27.1 + (c-b)/21.4 + (c-e)/23.3 + (c-f)/13.6) * 100;$$

$$OXI = (e-d)/11.7 - (d-c)/11.6 * 100 / HbI; \text{ and}$$

$$SO_2 = 100 * (OXI + 0.43) / 1.5$$

30

where a = absorption value at 500.9nm

b = absorption value at 528.1nm

c = absorption value at 549.5nm

d = absorption value at 561.1nm

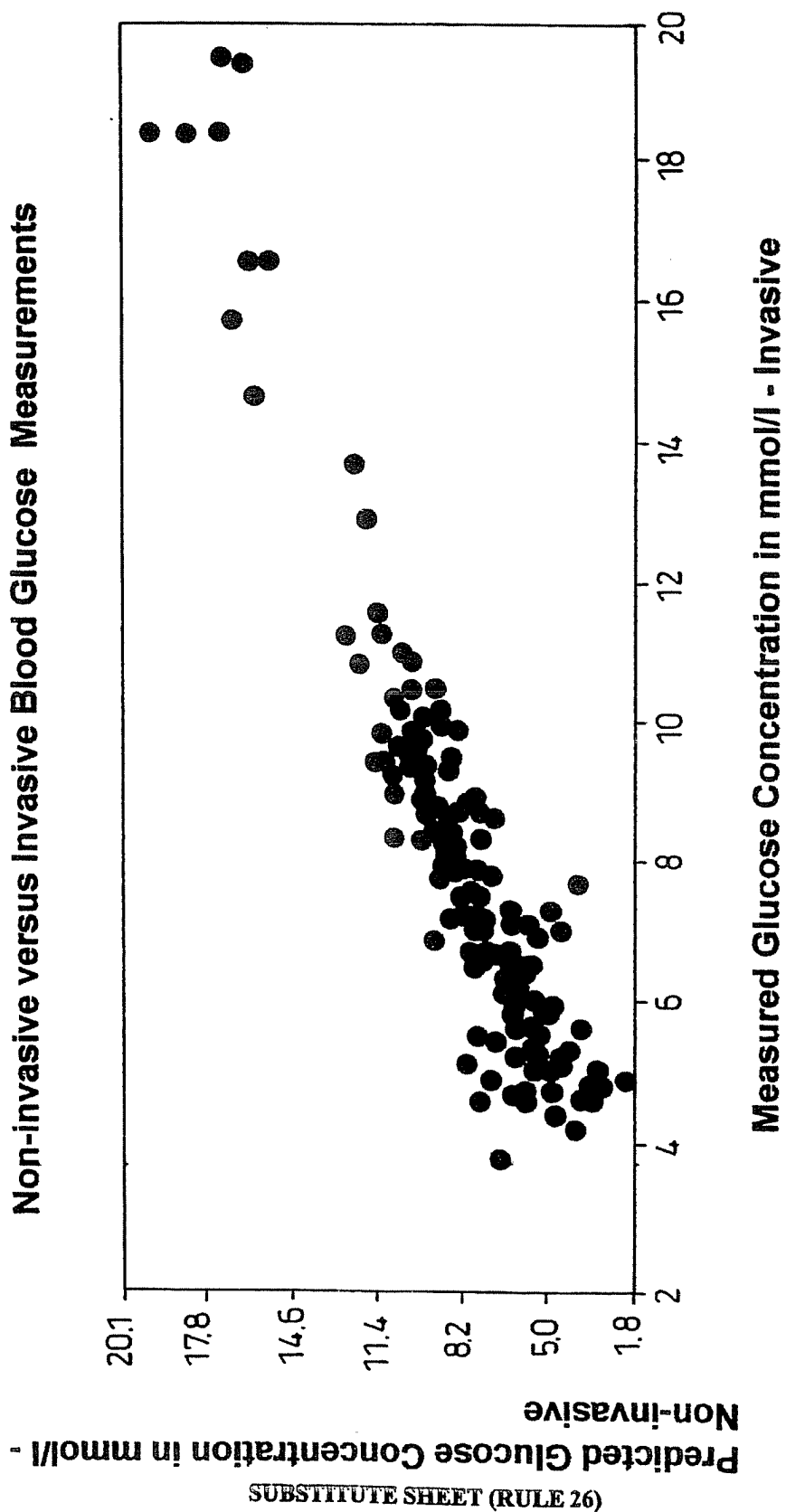
e = absorption value at 572.7nm

5

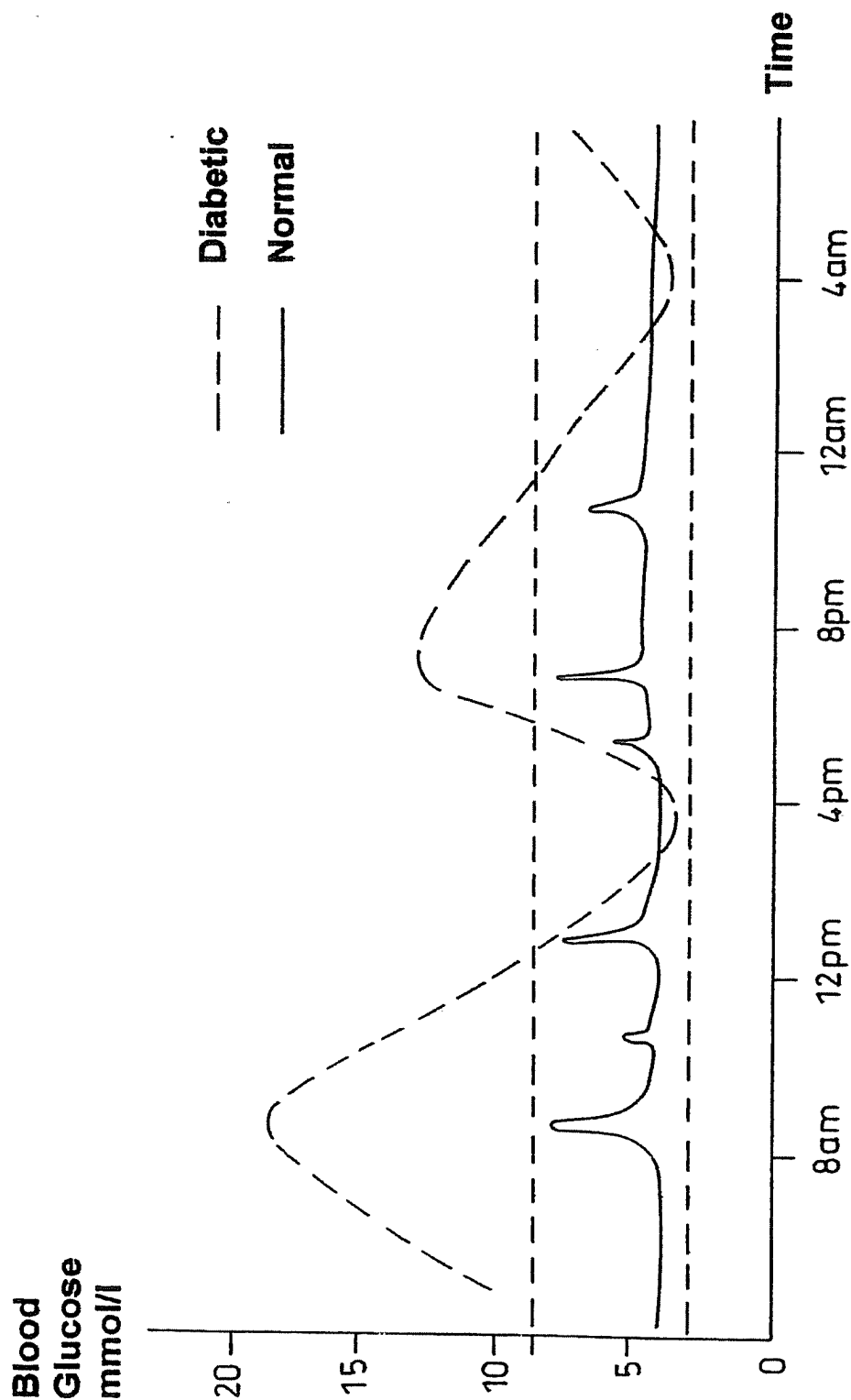
38. A device substantially as described with reference to the accompanying examples and drawings.

P36002WO.1

1/2



2/2



An example of blood glucose levels during the day

Fig. 1a

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 99/02127

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61B5/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 755 226 A (3M) 26 May 1998 (1998-05-26) the whole document	1-4,6,7, 9-11,15, 19-22, 24-31,38
X	WO 97 27800 A (DIASENSE) 7 August 1997 (1997-08-07) the whole document	1,5,12, 15-17

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

27 September 1999

Date of mailing of the international search report

05/10/1999

Name and mailing address of the ISA

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Lemercier, D

INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 99/ 02127

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 36,37
because they relate to subject matter not required to be searched by this Authority, namely:
Rule 39.1(iv) PCT - Program for computers
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims: it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 99/02127

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5755226 A	26-05-1998	US 5553615 A	10-09-1996
		EP 0742896 A	20-11-1996
		JP 9508291 T	26-08-1997
		WO 9520757 A	03-08-1995
WO 9727800 A	07-08-1997	AU 1846897 A	22-08-1997
		EP 0889703 A	13-01-1999